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Successful Treatment of Persistent Erythroid Aplasia Caused by Parvovirus B19 Infection in a Patient With Common Variable Immunodeficiency With Low-Dose Immunoglobulin

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Parvovirus B19 causes persistent erythroid aplasia in immunocompromised hosts. From April through July 1996, we encountered five adult patients presenting with reticulocytopenia and fever caused by parvovirus B19 infection. The reticulocyte count of four patients with normal immunity recovered within two weeks after the onset of fever. However, in the one remaining patient with common variable immunodeficiency (CVI), reticulocytopenia, and other symptoms including fever and the elevation of lactate dehydrogenase (LDH) levels persisted beyond 16 days of onset. Although the DNA of parvovirus B19 was detected in the peripheral blood of the CVI patient, neither immunoglobulin Ig-G nor Ig-M antibodies specific to the virus were detectable. We administered 50 mg/kg of Ig to the CVI patient for six days. The reticulocyte count recovered promptly on the sixth day of the treatment and parvovirus B19 DNA was not detectable 30 days after therapy. This indicates that although patients with CVI may be susceptible to persistent erythroid aplasia during an endemic of parvovirus B19, the complication can be treated successfully with relatively low-dose Ig. Am. J. Hematol. 60:222–224, 1999. **© 1999 Wiley-Liss, Inc.**

Key words: parvovirus B19; common variable immunodeficiency; low-dose immunoglobulin

INTRODUCTION

Human parvovirus B19 exhibits a remarkable tropism for erythroid progenitor cells. Because of its cytolytic effect, the virus causes an abrupt cessation of red cell production, leading to detectable reticulocytopenia. It has been suggested that neutralizing antibodies to viral antigens play a major role in limiting infection [1]. Persistent infection by parvovirus B19 can occur in immunocompromised hosts, especially in those with congenital immunodeficiency characterized by impaired immunoglobulin (Ig) production such as Nezelof syndrome [2] and hyper-Ig-M immunodeficiency [3], and can induce persistent erythroid aplasia. To restore erythropoiesis in these patients, high-dose Ig has been empirically administered. We report the successful treatment of persistent erythroid aplasia caused by parvovirus B19 infection in a patient with common variable immunodeficiency (CVI) by administering a relatively low-dose of Ig.

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CASE REPORT

A 28-year-old female who had suffered respiratory tract infection repeatedly over the last eight years presented with a productive cough in November 1995. Blood cell counts showed hemoglobin level of 11.0 g/dl, a white cell count of 22.4×10^9/l, and a platelet count of 268×10^9/l. She was diagnosed as having pneumonia and was treated with antibiotics. After the resolution of the pneumonia, the white cell count had decreased to 4.2×10^9/l. Laboratory examination revealed marked hypogammaglobulinemia (Ig-G, 130 mg/dl; Ig-A, 2 mg/dl; Ig-M, 25 mg/dl; Ig-D, below 1.0 mg/dl; and Ig-E, 2 IU/ml). T and B lymphocyte counts in peripheral blood as well as T lymphocyte responses to phytohemaggluti-

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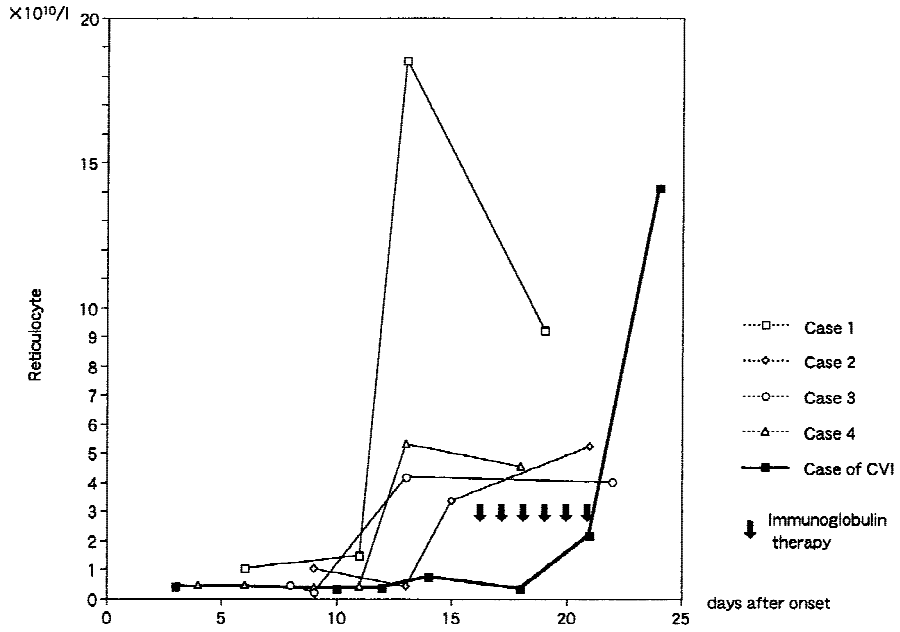

Fig. 1. Changes in the reticulocyte count of a patient with CVI and four patients with normal immunity (cases 1, 2, 3, 4) suffering parvovirus B19 infection.

nin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) were normal. No evidence of hematologic malignancies was detected. The patient had received vaccination for rubella, but no specific antibodies to the virus were detected. From the past history of recurrent infection after the age of 20 and our laboratory findings, CVI was diagnosed.

In July 1996, the patient became febrile with transient erythema of the trunk and upper limbs. Hematologic examination showed marked reticulocytopenia (3.3×10^9/l) and leukocytopenia (1.3×10^9/l). Laboratory data showed an elevation of lactate dehydrogenase (LDH) (470 IU/l) and CRP (4.5 mg/dl) levels. Bone marrow examination revealed the presence of giant erythroblasts and marked erythroid hypoplasia (a granulocyte/erythroblast ratio = 44.1). Prior to the presentation of this patient, we had encountered four patients with similar symptoms from April through May 1995. These patients were diagnosed from serological studies as having parvovirus B19 infection. Because the CVI patient lived in the same area as the other four patients, infection by the same virus was suspected. However, neither Ig-G nor Ig-M antibodies against parvovirus B19 were detected in the patient's serum.

Parvovirus B19 DNA was amplified from the patient's serum obtained four days after the onset of fever. Reticulocytopenia with elevated serum LDH levels and low-grade fever persisted for more than 16 days. Changes in the reticulocyte counts of the patient after admission were in sharp contrast to those of the previous four patients with normal immune functions (Fig. 1). Because the patient's hemoglobin level decreased from 10.4 g/dl to 6.6 g/dl, an Ig preparation (Venilon, Teijin, Osaka), 50 mg/kg/day, was administered intravenously for six days (Fig. 1). The Ig preparation contained anti-parvovirus B19 antibodies that were detectable using enzyme immunoassay. The reticulocyte count began to rise on the last day of Ig administration. Parvoviral DNA was no longer detectable two months after the Ig therapy. The hemoglobin level recovered to 10.9 g/dl three months after the Ig therapy.

DISCUSSION

In parvovirus B19 infection, humoral immune response such as the production of neutralizing antibodies to the capsid protein is thought to play a major role in limiting infection in humans [1]. Chronic pure red cell aplasia caused by persistent parvovirus infection develops in congenital [2–9] and acquired immunocompromised hosts [10–12]. Table I summarizes previous reports [2–9] of chronic red cell aplasia caused by a parvovirus B19 infection in cases of congenital immunodeficiency. Humoral immunodeficiency is a common feature of these patients. In the report of one patient by Davidson et al. [5], the underlying disease was CVI. This patient who was not treated with Ig preparations throughout his clinical course suffered prolonged infection for seven months despite normal values of Ig and Ig-G antibodies to parvovirus B19.

Our patient had decreased levels of all classes of Ig, normal counts of B and T lymphocytes in the peripheral blood, and normal T-cell responses to mitogens, all of which were compatible with CVI. The patient had repeat episodes of upper respiratory tract infection and failed to acquire immunity to the rubella virus after vaccination. Thus, impaired humoral immune response to parvovirus B19 was thought to predispose this patient to persistent erythroid aplasia.

TABLE I. Reports of Pure Red Cell Aplasia in Patients of Congenital Immunodeficiency Caused by Parvovirus B19 Infection*

Reference	Age/sex	Underlying disease	Duration of anemia	Humoral immunity	Dose of Ig-G
Kurtzman et al., 1987 [2]	2/male	Nezelof syndrome	2 months	Reduced Ig	Not mentioned
Kurtzman et al., 1989 [4]	24/male	Multiple immunologic abnormality	10 years	Reduced Ig-G	400 mg/kg
Davidson et al., 1989 [5]	21 months/male	Common variable immunodeficiency	7 months	Impaired humoral immunity	No therapy[a]
Gahr et al., 1991 [6]	12 months/female	Severe combined immunodeficiency	3 years	Reduced Ig	No therapy[b]
Hasle et al., 1994 [3]	8/male	Hyper Ig-M immunodeficiency	1 year	Reduced Ig-G	400 mg/kg
Tang et al., 1994 [7]	6/female	Combined immunodeficiency	4 weeks	Impaired humoral immunity	600 mg/kg
Nigro et al., 1994 [8]	3 months/male	Multiple immunologic abnormality	Not mentioned	Reduced Ig-G	400 mg/kg
Murray et al., 1996 [9]	7/male	Humoral immunodeficiency	10 weeks	Reduced Ig-G	500 mg/kg
This case	28/female	Common variable immunodeficiency		Reduced Ig	50 mg/kg

*Ig, immunoglobulin.
[a]Anemia didn't improved.
[b]This case had specific Ig-G for parvovirus B19, but anemia persisted seven months and then resolved.

During the limited period from April through July 1996, we encountered five patients with parvovirus infection including the CVI patient. Because the five patients lived in the same town, an endemic with a single viral strain was suspected. In an experimental infection of normal volunteers by parvovirus B19 [13], specific Ig-G antibody developed a week after the onset of fever and reticulocyte counts recovered within a week after that. Our four patients with normal humoral immunity did not suffer from persistent fever for more than a week and showed a rapid recovery from reticulocytopenia within two weeks. In contrast, the patient with CVI showed prolonged fever with marked reticulocytopenia. This was thought to be due to a lack of development of specific antibodies.

In patients with congenital immunodeficiency with chronic parvovirus infection, a dose of 400 mg/kg or more of Ig was reportedly required to eliminate the virus [4,7–9]. Similar doses of Ig were needed to treat chronic B19 infection associated with immunodeficiency due to HIV infection [10], chemotherapy [11], and allogeneic bone marrow transplantation [12]. We treated the CVI patient with a relatively low dose of Ig for six days to avoid the high cost of treatment.

Immediately after the treatment, the patient's fever resolved and the level of LDH declined. Reticulocyte count began to rise six days after treatment. Given the experimental data that reticulocytopenia resolved within a week after the development of neutralizing antibodies to parvovirus B19 in immunocompetent individuals, the recovery of our patient is probably ascribed to the administration of Ig preparations. This indicates that persistent erythroid aplasia caused by chronic parvovirus infection occurring in patients with CVI can be successfully treated with low-dose Ig in an early period of infection. Thus, when active signs of parvovirus infection such as fever and severe reticulocytopenia have persisted for more than two weeks in patients with CVI, administration of low-dose Ig is recommended.

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